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(54) Title: MIXTURES OF DRUG-OLIGOMER CONJUGATES COMPRISING POLYALKYLENE GLYCOL, USES THEREOF, AND METHODS OF MAKING SAME

(57) Abstract: A non-polydispersed mixture of conjugates in which each conjugate in the mixture comprises a drug coupled to an oligomer that includes a polyalkylene glycol moiety is disclosed. The mixture may exhibit higher in vivo activity than a polydispersed mixture of similar conjugates. The mixture may be more effective at surviving an in vitro model of intestinal digestion than polydispersed mixtures of similar conjugates. The mixture may result in less inter-subject variability than polydispersed mixtures of similar conjugates.

**MIXTURES OF DRUG-OLIGOMER
CONJUGATES COMPRISING POLYALKYLENE GLYCOL,
USES THEREOF, AND METHODS OF MAKING SAME**

Field Of The Invention

The present invention relates to drug-oligomer conjugates.

Background Of The Invention

Pharmaceutically active molecules such as proteins and polypeptides have been conjugated with polydispersed mixtures of polyethylene glycol or polydispersed mixtures of polyethylene glycol containing polymers to provide polydispersed mixtures of drug-oligomer conjugates. For example, U.S. Patent No. 4,179,337 to Davis et al. proposes conjugating polypeptides such as insulin with various polyethylene glycols such as MPEG-1900 and MPEG-5000 supplied by Union Carbide.

U.S. Patent No. 5,567,422 to Greenwald proposes the conjugation of biologically active nucleophiles with polyethylene glycols such as m-PEG-OH (Union Carbide), which has a number average molecular weight of 5,000 Daltons.

U.S. Patent No. 5,405,877 to Greenwald et al. proposes reacting bovine hemoglobin with thiazolidine thione activated PEG, which was prepared using m-PEG carboxylic acid having a number average molecular weight of 5,000 Daltons.

U.S. Patent No. 5,359,030 to Ekwuribe proposes conjugating polypeptides such as insulin with polyethylene glycol modified glycolipid polymers and polyethylene glycol modified fatty acid polymers. In this patent, the number average molecular weight of polymer resulting from each combination is preferred to be in the range of from about 500 to about 10,000 Daltons.

PEG is typically produced by base-catalyzed ring-opening polymerization of ethylene oxide. The reaction is initiated by adding ethylene oxide to ethylene glycol, with potassium

hydroxide as catalyst. This process results in a polydispersed mixture of polyethylene glycol polymers having a number average molecular weight within a given range of molecular weights. For example, PEG products offered by Sigma-Aldrich of Milwaukee, Wisconsin are provided in polydispersed mixtures such as PEG 400 (M_n 380-420); PEG 1,000 (M_n 950-1,050); PEG 1,500 (M_n 1,400-1,600); and PEG 2,000 (M_n 1,900-2,200).

It is desirable to provide non-polydispersed mixtures of drug-oligomer conjugates that comprises polyalkylene glycol.

Summary Of The Invention

A mixture of drug-oligomer conjugates comprising polyalkylene glycol according to embodiments of the present invention may exhibit higher *in vivo* activity than a polydispersed mixture of similar conjugates, where the polydispersed mixture has the same number average molecular weight as the mixture according to the present invention. This heightened activity may result in lower dosage requirements. Moreover, a mixture of drug-oligomer conjugates comprising polyalkylene glycol according to embodiments of the present invention may be more effective at surviving an *in vitro* model of intestinal digestion than polydispersed mixtures of similar conjugates. Furthermore, a mixture of drug-oligomer conjugates comprising polyalkylene glycol according to embodiments of the present invention may result in less inter-subject variability than polydispersed mixtures of similar conjugates.

According to embodiments of the present invention, a substantially monodispersed mixture of conjugates each comprising a drug coupled to an oligomer that comprises a polyalkylene glycol moiety is provided. The mixture preferably is a monodispersed mixture and, more preferably, is a purely monodispersed mixture. The polyalkylene glycol moiety preferably has at least 2, 3 or 4 polyalkylene glycol subunits. Most preferably, the polyalkylene glycol moiety preferably has at least 7 polyalkylene glycol subunits. The polyalkylene glycol moiety is preferably a polyethylene glycol moiety or polypropylene glycol moiety. The oligomer preferably further comprises a lipophilic moiety. The conjugate is preferably amphiphilically balanced such that the conjugate is aqueously soluble and able to penetrate biological membranes. The oligomer may comprise a first polyalkylene glycol moiety covalently coupled to the drug by a non-hydrolyzable bond and a second polyalkylene glycol moiety covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond.

According to other embodiments of the present invention, a substantially monodispersed mixture of conjugates is provided where each conjugate comprises a drug coupled to an oligomer including a polyalkylene glycol moiety, and the mixture has an *in vivo* activity that is greater than the *in vivo* activity of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the substantially monodispersed mixture.

According to still other embodiments of the present invention, a substantially monodispersed mixture of conjugates is provided where each conjugate comprises a drug coupled to an oligomer including a polyalkylene glycol moiety, and the mixture has an *in vitro* activity that is greater than the *in vitro* activity of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the substantially monodispersed mixture.

According to other embodiments of the present invention, a substantially monodispersed mixture of conjugates is provided where each conjugate comprises a drug coupled to an oligomer including a polyalkylene glycol moiety, and the mixture has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the substantially monodispersed mixture.

According to yet other embodiments of the present invention, a substantially monodispersed mixture of conjugates is provided where each conjugate comprises a drug coupled to an oligomer including a polyalkylene glycol moiety, and the mixture has an inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the substantially monodispersed mixture.

According to still other embodiments of the present invention, a mixture of conjugates is provided where each conjugate includes a drug coupled to an oligomer that comprises a polyalkylene glycol moiety, and the mixture has a molecular weight distribution with a standard deviation of less than about 22 Daltons.

According to yet other embodiments of the present invention, a mixture of conjugates is provided where each conjugate includes a drug coupled to an oligomer that comprises a polyalkylene glycol moiety, and the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 \sum_{i=1}^n N_i - \left(\sum_{i=1}^n N_i M_i \right)^2}$$

wherein:

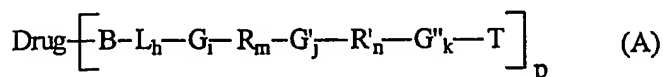
n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

5 M_i is the mass of the i^{th} molecule.

According to other embodiments of the present invention, a mixture of conjugates is provided in which each conjugate includes a drug coupled to an oligomer and has the same number of polyalkylene glycol subunits.

According to still other embodiments of the present invention, a mixture of conjugates
10 is provided in which each conjugate has the same molecular weight and has the formula:



wherein:

B is a bonding moiety;

L is a linker moiety;

15 G, G' and G'' are individually selected spacer moieties;

R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety;

h, i, j, k, m and n are individually 0 or 1, with the proviso that when R is the polyalkylene glycol moiety; m is 1, and when R' is the polyalkylene glycol moiety, n is 1; and
20

p is an integer from 1 to the number of nucleophilic residues on the drug.

Pharmaceutical compositions comprising conjugate mixtures of the present invention as well as methods of treating a disease state in a subject in need of such treatment by administering an effective amount of such pharmaceutical compositions are also provided.

25 Additionally, methods of synthesizing such conjugate mixtures are provided.

Drug-oligomer conjugate mixtures according to embodiments of the present invention may provide increased *in vivo* activity and/or lowered inter-subject variability and/or

decreased degradation by chymotrypsin when compared to conventional polydispersed drug-oligomer conjugate mixtures.

Brief Description of the Drawings

Figure 1 illustrates a generic scheme for synthesizing a mixture of activated polymers comprising a polyethylene glycol moiety and a fatty acid moiety according to embodiments of the present invention;

Figure 2 illustrates a scheme for synthesizing a mixture of mPEG according to embodiments of the present invention;

Figure 3 illustrates a scheme for synthesizing a mixture of activated mPEG7-hexyl oligomers according to embodiments of the present invention;

Figure 4 illustrates a scheme for synthesizing a mixture of activated mPEG7-octyl oligomers according to embodiments of the present invention;

Figure 5 illustrates a scheme for synthesizing a mixture of activated mPEG-decyl oligomers according to embodiments of the present invention;

Figure 6 illustrates a scheme for synthesizing a mixture of activated stearate-PEG6 oligomers according to embodiments of the present invention;

Figure 7 illustrates a scheme for synthesizing a mixture of activated stearate-PEG8 oligomers according to embodiments of the present invention;

Figure 8 illustrates a scheme for synthesizing a mixture of activated PEG3 oligomers according to embodiments of the present invention;

Figure 9 illustrates a scheme for synthesizing a mixture of activated palmitate-PEG3 oligomers according to embodiments of the present invention;

Figure 10 illustrates a scheme for synthesizing a mixture of activated PEG6 oligomers and conjugating human growth hormone with the activated PEG6 oligomers according to embodiments of the present invention;

Figure 11 illustrates a scheme for synthesizing various propylene glycol monomers according to embodiments of the present invention;

Figure 12 illustrates a scheme for synthesizing various propylene glycol polymers according to embodiments of the present invention;

Figure 13 illustrates a scheme for synthesizing various propylene glycol polymers according to embodiments of the present invention;

Figure 14 is an HPLC trace (HPLC gradient: 50% to 90% acetonitrile in 30 minutes) of the conjugation reaction illustrated in **Figure 10** using 2 equivalents of activated MPEG6 oligomers and 5 equivalents of activated MPEG6 oligomers;

Figure 15 is an HPLC trace (HPLC gradient: 0% to 95% acetonitrile in 20 minutes) of the conjugation reaction illustrated in **Figure 10** using 30 equivalents of activated MPEG6 oligomers;

Figure 16 is a MALDI spectra of the conjugation reaction illustrated in **Figure 10** using 2 equivalents of activated MPEG6 oligomers;

Figure 17 is an HPLC trace (HPLC gradient: 50% to 70% acetonitrile in 30 minutes) illustrating a partial purification of the product of the conjugation reaction of **Figure 10** using 5 equivalents of activated MPEG6 oligomers;

Figure 18 is a MALDI spectra of fraction B from the partial purification illustrated in **Figure 17**;

Figure 19 is a MALDI spectra of fraction C from the partial purification illustrated in **Figure 17**;

Figure 20 is a MALDI spectra of fractions D and E from the partial purification illustrated in **Figure 17**;

Figure 21 is an electrospray spectra of fraction E from the partial purification illustrated in **Figure 17**;

Figure 22 is an electrospray spectra of the reaction mixture from the conjugation reaction illustrated in **Figure 10** using 30 equivalents of activated MPEG6 oligomers;

Figure 23 is an HPLC trace of a conjugation reaction of human growth hormone with the activated oligomer of **Figure 9**;

Figure 24 is an HPLC trace of a conjugation reaction using one equivalent of human growth hormone and two equivalents of the activated oligomer of **Figure 9** according to the present invention compared with an HPLC trace of human growth hormone, which does not form part of the present invention;

Figure 25 is an HPLC trace of a conjugation reaction using one equivalent of human growth hormone and five equivalents of the activated oligomer of **Figure 8** according to the present invention compared with an HPLC trace of human growth hormone, which does not form part of the present invention;

Figure 26 is a MALDI spectra of the fraction corresponding to the left half of the peak in the conjugation HPLC trace of Figure 25;

Figure 27 is a MALDI spectra of the fraction corresponding to the right half of the peak in the conjugation HPLC trace of Figure 25;

5 Figure 28 is an HPLC trace of a conjugation reaction using one equivalent of human growth hormone and 9 equivalents of the activated oligomer of Figure 8 according to the present invention compared with an HPLC trace of human growth hormone, which does not form part of the present invention;

Figure 29 illustrates a comparison of results obtained with a Cytosensor®
10 Microphysiometer, which provides an indication of the activity of a compound, for mixtures of insulin-oligomer conjugates according to embodiments of the present invention compared with polydispersed conjugate mixtures and insulin, which are provided for comparison purposes only and do not form part of the invention;

Figure 30 illustrates a comparison of chymotrypsin degradation of insulin-oligomer
15 conjugates according to embodiments of the present invention with a conventional polydispersed mixture of insulin-oligomer conjugates, which is provided for comparison purposes only and does not form part of the invention;

Figure 31 illustrates the effect of a mixture of mPEG7-hexyl-insulin, monoconjugate, according to embodiments of the present invention on plasma glucose in fasted beagles;

20 Figure 32 illustrates, for comparison purposes, the effect of a polydispersed mixture of mPEG7_{avg}-hexyl-insulin, monoconjugate, which is not part of the present invention, on plasma glucose in fasted beagles;

Figure 33 illustrates the inter-subject variability of a mixture of mPEG4-hexyl-insulin monoconjugates according to embodiments of the present invention administered to fasted
25 beagles;

Figure 34 illustrates the inter-subject variability of a mixture of mPEG7-hexyl-insulin monoconjugates according to embodiments of the present invention administered to fasted beagles;

Figure 35 illustrates the inter-subject variability for a mixture of mPEG10-hexyl-
30 insulin monoconjugates according to embodiments of the present invention administered to fasted beagles;

Figure 36 illustrates, for comparison purposes, the inter-subject variability of a polydispersed mixture of mPEG7_{avg}-hexyl-insulin monoconjugates, which is not part of the present invention, administered to fasted beagles;

5 Figure 37 illustrates a comparison of the average AUCs for various monodispersed mixtures of calcitonin-oligomer conjugates according to embodiments of the present invention with non-conjugated calcitonin, which is provided for comparison purposes only and does not form part of the invention;

10 Figure 38 illustrates dose-response curves where the response is measured as a percentage of the maximum possible response for a mixture of mPEG7-octyl-calcitonin diconjugates according to embodiments of the present invention compared with calcitonin, which is provided for comparison purposes and is not a part of the present invention;

Figure 39 illustrates a dose-response curve after oral administration of a mixture of mPEG7-octyl-calcitonin diconjugates according to embodiments of the present invention;

15 Figure 40 illustrates a dose-response curve after subcutaneous administration of a mixture of mPEG7-octyl-calcitonin diconjugates according to embodiments of the present invention;

Figure 41 illustrates a dose-response curve after subcutaneous administration of salmon calcitonin, which is provided for comparison purposes and is not part of the present invention;

20 Figure 42 illustrates a bar graph denoting the activity as determined by luciferase assay of mixtures of growth hormone conjugates according to embodiments of the present invention compared with the activity of human growth hormone standards, which are provided for comparison purposes only and do not form part of the present invention; and

25 Figure 43 illustrates a bar graph denoting the activity as determined by luciferase assay of mixtures of growth hormone conjugates according to embodiments of the present invention compared with the activity of human growth hormone standards, which are provided for comparison purposes only and do not form part of the present invention.

Detailed Description Of Preferred Embodiments

30 The invention will now be described with respect to preferred embodiments described herein. It should be appreciated however that these embodiments are for the purpose of

illustrating the invention, and are not to be construed as limiting the scope of the invention as defined by the claims.

As used herein, the term "non-polydispersed" is used to describe a mixture of compounds having a dispersity that is in contrast to the polydispersed mixtures described in U.S. Patent No. 4,179,337 to Davis et al.; U.S. Patent No. 5,567,422 to Greenwald; U.S. Patent No. 5,405,877 to Greenwald et al.; and U.S. Patent No. 5,359,030 to Ekwuribe.

As used herein, the term "substantially monodispersed" is used to describe a mixture of compounds wherein at least about 95 percent of the compounds in the mixture have the same molecular weight.

As used herein, the term "monodispersed" is used to describe a mixture of compounds wherein about 100 percent of the compounds in the mixture have the same molecular weight.

As used herein, the term "substantially purely monodispersed" is used to describe a mixture of compounds wherein at least about 95 percent of the compounds in the mixture have the same molecular weight and same molecular structure. Thus, a substantially purely monodispersed mixture is a substantially monodispersed mixture, but a substantially monodispersed mixture is not necessarily a substantially purely monodispersed mixture.

As used herein, the term "purely monodispersed" is used to describe a mixture of compounds wherein about 100 percent of the compounds in the mixture have the same molecular weight and have the same molecular structure. Thus, a purely monodispersed mixture is a monodispersed mixture, but a monodispersed mixture is not necessarily a purely monodispersed mixture.

As used herein, the term "weight average molecular weight" is defined as the sum of the products of the weight fraction for a given molecule in the mixture times the mass of the molecule for each molecule in the mixture. The "weight average molecular weight" is represented by the symbol M_w .

As used herein, the term "number average molecular weight" is defined as the total weight of a mixture divided by the number of molecules in the mixture and is represented by the symbol M_n .

As used herein, the term "dispersity coefficient" (DC) is defined by the formula:

$$DC = \frac{\left(\sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 \sum_{i=1}^n N_i - \left(\sum_{i=1}^n N_i M_i \right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

5 M_i is the mass of the i^{th} molecule.

As used herein, the term "intra-subject variability" means the variability in activity occurring within the same subject when the subject is administered the same dose of a drug or pharmaceutical composition at different times.

10 As used herein, the term "inter-subject variability" means the variability in activity between two or more subjects when each subject is administered the same dose of a given drug or pharmaceutical formulation.

As used herein, the term "polyalkylene glycol" refers to straight or branched polyalkylene glycol polymers such as polyethylene glycol, polypropylene glycol, and polybutylene glycol, and includes the monoalkylether of the polyalkylene glycol. The term
15 "polyalkylene glycol subunit" refers to a single polyalkylene glycol unit. For example, a polyethylene glycol subunit would be $-O-CH_2-CH_2-O-$.

As used herein, the term "lipophilic" means the ability to dissolve in lipids and/or the ability to penetrate, interact with and/or traverse biological membranes, and the term, "lipophilic moiety" or "lipophile" means a moiety which is lipophilic and/or which, when
20 attached to another chemical entity, increases the lipophilicity of such chemical entity. Examples of lipophilic moieties include, but are not limited to, alkyls, fatty acids, esters of fatty acids, cholesteryl, adamantyl and the like.

As used herein, the term "lower alkyl" refers to substituted or unsubstituted alkyl moieties having from 1 to 5 carbon atoms.

25 As used herein, the term "higher alkyl" refers to substituted or unsubstituted alkyl moieties having 6 or more carbon atoms.

As used herein, the term "drug" refers to any therapeutic compound that is conjugatable in the manner of the present invention. Representative non-limiting classes of therapeutic compounds useful in the present invention include those falling into the following

therapeutic categories: ACE-inhibitors; anti-anginal drugs; anti-arrhythmias; anti-asthmatics; anti-cholesterolemics; anti-convulsants; anti-depressants; anti-diarrhea preparations; anti-histamines; anti-hypertensive drugs; anti-infectives; anti-inflammatory agents; anti-lipid agents; anti-manics; anti-nauseants; anti-stroke agents; anti-thyroid preparations; anti-tumor
 5 drugs; anti-tussives; anti-uricemic drugs; anti-viral agents; acne drugs; alkaloids; amino acid preparations; anabolic drugs; analgesics; anesthetics; angiogenesis inhibitors; antacids; anti-arthritis; antibiotics; anticoagulants; antiemetics; antiobesity drugs; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotic drugs; anxiolytic agents; appetite stimulants; appetite suppressants; beta blocking agents; bronchodilators; cardiovascular
 10 agents; cerebral dilators; chelating agents; cholecystokinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypnotics;
 15 hypoglycemic agents; laxatives; migraine treatments; mineral supplements; mucolytics; narcotics; neuroleptics; neuromuscular drugs; NSAIDS; nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; and
 20 wound healing agents.

The drug is preferably a polypeptide. Non-limiting examples of polypeptides that may be useful in the present invention include the following:

Adrenocorticotrophic hormone (ACTH) peptides including, but not limited to, ACTH, human; ACTH 1-10; ACTH 1-13, human; ACTH 1-16, human; ACTH 1-17; ACTH 1-24,
 25 human; ACTH 4-10; ACTH 4-11; ACTH 6-24; ACTH 7-38, human; ACTH 18-39, human; ACTH, rat; ACTH 12-39, rat; beta-cell tropin (ACTH 22-39); biotinyl-ACTH 1-24, human; biotinyl-ACTH 7-38, human; corticostatin, human; corticostatin, rabbit; [Met(02)⁴, DLys⁸, Phe⁹] ACTH 4-9, human; [Met(0)⁴, DLys⁸, Phe⁹] ACTH 4-9, human; N-acetyl, ACTH 1-17, human; and ebitatide.

30 Adrenomedullin peptides including, but not limited to, adrenomedullin, adrenomedullin 1-52, human; adrenomedullin 1-12, human; adrenomedullin 13-52, human; adrenomedullin 22-52, human; pro-adrenomedullin 45-92, human; pro-adrenomedullin 153-

185, human; adrenomedullin 1-52, porcine; pro-adrenomedullin (N-20), porcine; adrenomedullin 1-50, rat; adrenomedullin 11-50, rat; and proAM-N20 (proadrenomedullin N-terminal 20 peptide), rat.

Allatostatin peptides including, but not limited to, allatostatin I; allatostatin II;
 5 allatostatin III; and allatostatin IV.

Amylin peptides including, but not limited to, acetyl-amylin 8-37, human; acetylated amylin 8-37, rat; AC187 amylin antagonist; AC253 amylin antagonist; AC625 amylin antagonist; amylin 8-37, human; amylin (IAPP), cat; amylin (insulinoma or islet amyloid polypeptide(IAPP)); amylin amide, human; amylin 1-13 (diabetes-associated peptide 1-13),
 10 human; amylin 20-29 (IAPP 20-29), human; AC625 amylin antagonist; amylin 8-37, human; amylin (IAPP), cat; amylin, rat; amylin 8-37, rat; biotinyl-amylin, rat; and biotinyl-amylin amide, human.

Amyloid beta-protein fragment peptides including, but not limited to, Alzheimer's disease beta-protein 12-28 (SP17); amyloid beta-protein 25-35; amyloid beta/A4-protein precursor 328-332; amyloid beta/A4 protein precursor (APP) 319-335; amyloid beta-protein
 15 1-43; amyloid beta-protein 1-42; amyloid beta-protein 1-40; amyloid beta-protein 10-20; amyloid beta-protein 22-35; Alzheimer's disease beta-protein (SP28); beta-amyloid peptide 1-42, rat; beta-amyloid peptide 1-40, rat; beta-amyloid 1-11; beta-amyloid 31-35; beta-amyloid 32-35; beta-amyloid 35-25; beta-amyloid/A4 protein precursor 96-110; beta-amyloid
 20 precursor protein 657-676; beta-amyloid 1-38; [Gln¹¹]-Alzheimer's disease beta-protein; [Gln¹¹]-beta-amyloid 1-40; [Gln²²]-beta-amyloid 6-40; non-A beta component of Alzheimer's disease amyloid (NAC); P3, (A beta 17-40) Alzheimer's disease amyloid β -peptide; and SAP (serum amyloid P component) 194-204.

Angiotensin peptides including, but not limited to, A-779; Ala-Pro-Gly-angiotensin
 25 II; [Ile³,Val⁵]-angiotensin II; angiotensin III antipeptide; angiogenin fragment 108-122; angiogenin fragment 108-123; angiotensin I converting enzyme inhibitor; angiotensin I, human; angiotensin I converting enzyme substrate; angiotensin 11-7, human; angiopeptin; angiotensin II, human; angiotensin II antipeptide; angiotensin II 1-4, human; angiotensin II 3-8, human; angiotensin II 4-8, human; angiotensin II 5-8, human; angiotensin III ([Des-Asp¹]-
 30 angiotensin II), human; angiotensin III inhibitor ([Ile⁷]-angiotensin III); angiotensin-converting enzyme inhibitor (Neothunnus macropterus); [Asn¹, Val⁵]-angiotensin I, goosefish; [Asn¹, Val⁵, Asn⁹]-angiotensin I, salmon; [Asn¹, Val⁵, Gly⁹]-angiotensin I, eel;

[Asn¹, Val⁵]-angiotensin I 1-7, eel, goosefish, salmon; [Asn¹, Val⁵]-angiotensin II; biotinyl-angiotensin I, human; biotinyl-angiotensin II, human; biotinyl-Ala-Ala-Ala-angiotensin II; [Des-Asp¹]-angiotensin I, human; [p-aminophenylalanine⁶]-angiotensin II; renin substrate (angiotensinogen 1-13), human; preangiotensinogen 1-14 (renin substrate tetradecapeptide), human; renin substrate tetradecapeptide (angiotensinogen 1-14), porcine; [Sar¹]-angiotensin II, [Sar¹]-angiotensin II 1-7 amide; [Sar¹, Ala⁸]-angiotensin II; [Sar¹, Ile⁸]-angiotensin II; [Sar¹, Thr⁸]-angiotensin II; [Sar¹, Tyr(Me)⁴]-angiotensin II (Sarmesin); [Sar¹, Val⁵, Ala⁸]-angiotensin II; [Sar¹, Ile⁷]-angiotensin III; synthetic tetradecapeptide renin substrate (No. 2); [Val⁴]-angiotensin III; [Val⁵]-angiotensin II; [Val⁵]-angiotensin I, human; [Val⁵]-angiotensin I; [Val⁵, Asn⁹]-angiotensin I, bullfrog; and [Val⁵, Ser⁹]-angiotensin I, fowl.

Antibiotic peptides including, but not limited to, Ac-SQNY; bactenecin, bovine; CAP 37 (20-44); carbomethoxycarbonyl-DPro-DPhe-OBzl; CD36 peptide P 139-155; CD36 peptide P 93-110; cecropin A-melittin hybrid peptide [CA(1-7)M(2-9)NH₂]; cecropin B, free acid; CYS(Bzl)₈₄ CD fragment 81-92; defensin (human) HNP-2; dermaseptin; immunostimulating peptide, human; lactoferricin, bovine (BLFC); and magainin spacer.

Antigenic polypeptides, which can elicit an enhanced immune response, enhance an immune response and or cause an immunizingly effective response to diseases and/or disease causing agents including, but not limited to, adenoviruses; anthrax; Bordetella pertussus; botulism; bovine rhinotracheitis; Branhamella catarrhalis; canine hepatitis; canine distemper; Chlamydiae; cholera; coccidiomycosis; cowpox; cytomegalovirus; Dengue fever; dengue toxoplasmosis; diphtheria; encephalitis; enterotoxigenic E. coli; Epstein Barr virus; equine encephalitis; equine infectious anemia; equine influenza; equine pneumonia; equine rhinovirus; Escherichia coli; feline leukemia; flavivirus; globulin; haemophilus influenza type b; Haemophilus influenzae; Haemophilus pertussis; Helicobacter pylori; hemophilus; hepatitis; hepatitis A; hepatitis B; Hepatitis C; herpes viruses; HIV; HIV- 1 viruses; HIV-2 viruses; HTLV; influenza; Japanese encephalitis; Klebsiellae species; Legionella pneumophila; leishmania; leprosy; lyme disease; malaria immunogen; measles; meningitis; meningococcal; Meningococcal polysaccharide group A; Meningococcal polysaccharide group C; mumps; mumps virus; mycobacteria; Mycobacterium tuberculosis; Neisseria; Neisseria gonorrhea; Neisseria meningitidis; ovine blue tongue; ovine encephalitis; papilloma; parainfluenza; paramyxoviruses; Pertussis; plague; pneumococcus; Pneumocystis carinii; pneumonia; poliovirus; proteus species; Pseudomonas aeruginosa; rabies; respiratory

syncytial virus; rotavirus; rubella; salmonellae; schistosomiasis; shigellae; simian immunodeficiency virus; smallpox; *Staphylococcus aureus*; *Staphylococcus* species; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Streptococcus* species; swine influenza; tetanus; *Treponema pallidum*; typhoid; vaccinia; varicella-zoster virus; and vibrio cholerae.

- 5 Anti-microbial peptides including, but not limited to, buforin I; buforin II; cecropin A; cecropin B; cecropin P1, porcine; gaegurin 2 (*Rana rugosa*); gaegurin 5 (*Rana rugosa*); indolicidin; protegrin-(PG)-I; magainin 1; and magainin 2; and T-22 [Tyr^{5,12}, Lys⁷]-polyphemusin II peptide.

- 10 Apoptosis related peptides including, but not limited to, Alzheimer's disease beta-protein (SP28); calpain inhibitor peptide; caspase-1 inhibitor V; caspase-3, substrate IV; caspase-1 inhibitor I, cell-permeable; caspase-1 inhibitor VI; caspase-3 substrate III, fluorogenic; caspase-1 substrate V, fluorogenic; caspase-3 inhibitor I, cell-permeable; caspase-6 ICE inhibitor III; [Des-Ac, biotin]-ICE inhibitor III; IL-1 B converting enzyme (ICE) inhibitor II; IL-1 B converting enzyme (ICE) substrate IV; MDL 28170; and MG-132.

- 15 Atrial natriuretic peptides including, but not limited to, alpha-ANP (alpha-chANP), chicken; anantin; ANP 1-11, rat; ANP 8-30, frog; ANP 11-30, frog; ANP-21 (fANP-21), frog; ANP-24 (fANP-24), frog; ANP-30, frog; ANP fragment 5-28, human, canine; ANP-7-23, human; ANP fragment 7-28, human, canine; alpha-atrial natriuretic polypeptide 1-28, human, canine; A71915, rat; atrial natriuretic factor 8-33, rat; atrial natriuretic polypeptide 3-20 28, human; atrial natriuretic polypeptide 4-28, human, canine; atrial natriuretic polypeptide 5-27; human; atrial natriuretic peptide (ANP), eel; atriopeptin I, rat, rabbit, mouse; atriopeptin II, rat, rabbit, mouse; atriopeptin III, rat, rabbit, mouse; atrial natriuretic factor (rANF), rat, auriculin A (rat ANF 126-149); auriculin B (rat ANF 126-150); beta-ANP (1-28, dimer, antiparallel); beta-rANF 17-48; biotinyl-alpha-ANP 1-28, human, canine; biotinyl-atrial 25 natriuretic factor (biotinyl-rANF), rat; cardiodilatin 1-16, human; C-ANF 4-23, rat; Des-[Cys¹⁰⁵, Cys¹²¹]-atrial natriuretic factor 104-126, rat; [Met(O)¹²] ANP 1-28, human; [Mpr⁷, DAla⁹]ANP 7-28, amide, rat; prepro-ANF 104-116, human; prepro-ANF 26-55 (proANF 1-30), human; prepro-ANF 56-92 (proANF 31-67), human; prepro-ANF 104-123, human; [Tyr⁰]-atriopeptin I, rat, rabbit, mouse; [Tyr⁰]-atriopeptin II, rat, rabbit, mouse; 30 [Tyr⁰]-prepro ANF 104-123, human; urodilatin (CDD/ANP 95-126); ventricular natriuretic peptide (VNP), eel; and ventricular natriuretic peptide (VNP), rainbow trout.

Bag cell peptides including, but not limited to, alpha bag cell peptide; alpha-bag cell peptide 1-9; alpha-bag cell peptide 1-8; alpha-bag cell peptide 1-7; beta-bag cell factor; and gamma-bag cell factor.

Bombesin peptides including, but not limited to, alpha-s1 casein 101-123 (bovine milk); biotinyl-bombesin; bombesin 8-14; bombesin; [Leu¹³-psi (CH₂NH)Leu¹⁴]-bombesin; [D-Phe⁶, Des-Met¹⁴]-bombesin 6-14 ethylamide; [DPhe¹²] bombesin; [DPhe¹²,Leu¹⁴]-bombesin; [Tyr⁴]-bombesin; and [Tyr⁴,DPhe¹²]-bombesin.

Bone GLA peptides (BGP) including, but not limited to, bone GLA protein; bone GLA protein 45-49; [Glu¹⁷, Gla^{21,24}]-osteocalcin 1-49, human; myclopeptide -2 (MP-2); osteocalcin 1-49 human; osteocalcin 37-49, human; and [Tyr³⁸, Phe^{42,46}] bone GLA protein 38-49, human.

Bradykinin peptides including, but not limited to, [Ala^{2,6}, des-Pro³]-bradykinin; bradykinin; bradykinin (Bowfin. Gar); bradykinin potentiating peptide; bradykinin 1-3; bradykinin 1-5; bradykinin 1-6; bradykinin 1-7; bradykinin 2-7; bradykinin 2-9; [DPhe⁷] bradykinin; [Des-Arg⁹]-bradykinin; [Des-Arg¹⁰]-Lys-bradykinin ([Des-Arg¹⁰]-kallidin); [D-N-Me-Phe⁷]-bradykinin; [Des-Arg⁹, Leu⁸]-bradykinin; Lys-bradykinin (kallidin); Lys-[Des-Arg⁹,Leu⁸]-bradykinin ([Des-Arg¹⁰,Leu⁹]-kallidin); [Lys⁰-Hyp³]-bradykinin; ovokinin; [Lys⁰, Ala³]-bradykinin; Met-Lys-bradykinin; peptide K12 bradykinin potentiating peptide; [(pCl)Phe^{5,8}]-bradykinin; T-kinin (Ile-Ser-bradykinin); [Thi^{5,8}, D-Phe⁷]-bradykinin; [Tyr⁰]-bradykinin; [Tyr⁵]-bradykinin; [Tyr⁸]-bradykinin; and kallikrein.

Brain natriuretic peptides (BNP) including, but not limited to, BNP 32, canine; BNP-like Peptide, eel; BNP-32, human; BNP-45, mouse; BNP-26, porcine; BNP-32, porcine; biotinyl-BNP-32, porcine; BNP-32, rat; biotinyl-BNP-32, rat; BNP-45 (BNP 51-95, 5K cardiac natriuretic peptide), rat; and [Tyr⁰]-BNP 1-32, human.

C-peptides including, but not limited to, C-peptide; and [Tyr⁰]-C-peptide, human.

C-type natriuretic peptides (CNP) including, but not limited to, C-type natriuretic peptide, chicken; C-type natriuretic peptide-22 (CNP-22), porcine, rat, human; C-type natriuretic peptide-53 (CNP-53), human; C-type natriuretic peptide-53 (CNP-53), porcine, rat; C-type natriuretic peptide-53 (porcine, rat) 1-29 (CNP-53 1-29); prepro-CNP 1-27, rat; prepro-CNP 30-50, porcine, rat; vasonatrin peptide (VNP); and [Tyr⁰]-C-type natriuretic peptide-22 ([Tyr⁰]-CNP-22).

Calcitonin peptides including, but not limited to, biotinyl-calcitonin, human; biotinyl-calcitonin, rat; biotinyl-calcitonin, salmon; calcitonin, chicken; calcitonin, eel; calcitonin, human; calcitonin, porcine; calcitonin, rat; calcitonin, salmon; calcitonin 1-7, human; calcitonin 8-32, salmon; katalcalcin (PDN-21) (C-procalcitonin); and N-proCT (amino-terminal procalcitonin cleavage peptide), human.

Calcitonin gene related peptides (CGRP) including, but not limited to, acetyl-alpha-CGRP 19-37, human; alpha-CGRP 19-37, human; alpha-CGRP 23-37, human; biotinyl-CGRP, human; biotinyl-CGRP II, human; biotinyl-CGRP, rat; beta-CGRP, rat; biotinyl-beta-CGRP, rat; CGRP, rat; CGRP, human; calcitonin C-terminal adjacent peptide; CGRP 1-19, human; CGRP 20-37, human; CGRP 8-37, human; CGRP II, human; CGRP, rat; CGRP 8-37, rat; CGRP 29-37, rat; CGRP 30-37, rat; CGRP 31-37, rat; CGRP 32-37, rat; CGRP 33-37, rat; CGRP 31-37, rat; ([Cys(Acm)^{2,7}]-CGRP; elcatonin; [Tyr⁰]-CGRP, human; [Tyr⁰]-CGRP II, human; [Tyr⁰]-CGRP 28-37, rat; [Tyr⁰]-CGRP, rat; and [Tyr²²]-CGRP 22-37, rat.

CART peptides including, but not limited to, CART, human; CART 55-102, human; CART, rat; and CART 55-102, rat.

Casomorphin peptides including, but not limited to, beta-casomorphin, human; beta-casomorphin 1-3; beta-casomorphin 1-3, amide; beta-casomorphin, bovine; beta-casomorphin 1-4, bovine; beta-casomorphin 1-5, bovine; beta-casomorphin 1-5, amide, bovine; beta-casomorphin 1-6, bovine; [DAla²]-beta-casomorphin 1-3, amide, bovine; [DAla²,Hyp⁴,Tyr⁵]-beta-casomorphin 1-5 amide; [DAla²,DPro⁴,Tyr⁵]-beta-casomorphin 1-5, amide; [DAla²,Tyr⁵]-beta-casomorphin 1-5, amide, bovine; [DAla^{2,4},Tyr⁵]-beta-casomorphin 1-5, amide, bovine; [DAla², (pCl)Phe³]-beta-casomorphin, amide, bovine; [DAla²]-beta-casomorphin 1-4, amide, bovine; [DAla²]-beta-casomorphin 1-5, bovine; [DAla²]-beta-casomorphin 1-5, amide, bovine; [DAla²,Met⁵]-beta-casomorphin 1-5, bovine; [DPro²]-beta-casomorphin 1-5, amide, bovine; [DAla²]-beta-casomorphin 1-6, bovine; [DPro²]-beta-casomorphin 1-4, amide; [Des-Tyr¹]-beta-casomorphin, bovine; [DAla^{2,4},Tyr⁵]-beta-casomorphin 1-5, amide, bovine; [DAla², (pCl)Phe³]-beta-casomorphin, amide, bovine; [DAla²]-beta-casomorphin 1-4, amide, bovine; [DAla²]-beta-casomorphin 1-5, bovine; [DAla²]-beta-casomorphin 1-5, amide, bovine; [DAla²,Met⁵]-beta-casomorphin 1-5, bovine; [DPro²]-beta-casomorphin 1-5, amide, bovine; [DAla²]-beta-casomorphin 1-6, bovine; [DPro²]-beta-casomorphin 1-4, amide; [Des-Tyr¹]-beta-casomorphin, bovine; and [Val³]-beta-casomorphin 1-4, amide, bovine.

Chemotactic peptides including, but not limited to, defensin 1 (human) HNP-1 (human neutrophil peptide-1); and N-formyl-Met-Leu-Phe.

Cholecystokinin (CCK) peptides including, but not limited to, caerulein; cholecystokinin; cholecystokinin-pancreozymin; CCK-33, human; cholecystokinin octapeptide 1-4 (non-sulfated) (CCK 26-29, unsulfated); cholecystokinin octapeptide (CCK 26-33); cholecystokinin octapeptide (non-sulfated) (CCK 26-33, unsulfated); cholecystokinin heptapeptide (CCK 27-33); cholecystokinin tetrapeptide (CCK 30-33); CCK-33, porcine; CR 1 409, cholecystokinin antagonist; CCK flanking peptide (unsulfated); N-acetyl cholecystokinin, CCK 26-30, sulfated; N-acetyl cholecystokinin, CCK 26-31, sulfated; N-acetyl cholecystokinin, CCK 26-31, non-sulfated; prepro CCK fragment V-9-M; and proglumide.

Colony-stimulating factor peptides including, but not limited to, colony-stimulating factor (CSF); GM-CSF; M-CSF; and G-CSF.

Corticotropin releasing factor (CRF) peptides including, but not limited to, astressin; alpha-helical CRF 12-41; biotinyl-CRF, ovine; biotinyl-CRF, human, rat; CRF, bovine; CRF, human, rat; CRF, ovine; CRF, porcine; [Cys²¹]-CRF, human, rat; CRF antagonist (alpha-helical CRF 9-41); CRF 6-33, human, rat; [DPro⁵]-CRF, human, rat; [D-Phe¹², Nle^{21,38}]-CRF 12-41, human, rat; eosinophilotactic peptide; [Met(0)²¹]-CRF, ovine; [Nle²¹, Tyr³²]-CRF, ovine; prepro CRF 125-151, human; sauvagine, frog; [Tyr⁰]-CRF, human, rat; [Tyr⁰]-CRF, ovine; [Tyr⁰]-CRF 34-41, ovine; [Tyr⁰]-urocortin; urocortin amide, human; urocortin, rat; urotensin I (*Catostomus commersoni*); urotensin II; and urotensin II (*Rana ridibunda*).

Cortistatin peptides including, but not limited to, cortistatin 29; cortistatin 29 (1-13); [Tyr⁰]-cortistatin 29; pro-cortistatin 28-47; and pro-cortistatin 51-81.

Cytokine peptides including, but not limited to, tumor necrosis factor; and tumor necrosis factor- β (TNF- β).

Dermorphin peptides including, but not limited to, dermorphin and dermorphin analog 1-4.

Dynorphin peptides including, but not limited to, big dynorphin (prodynorphin 209-240), porcine; biotinyl-dynorphin A (biotinyl-prodynorphin 209-225); [DAla², DArg⁶]-dynorphin A 1-13, porcine; [D-Ala²]-dynorphin A, porcine; [D-Ala²]-dynorphin A amide, porcine; [D-Ala²]-dynorphin A 1-13, amide, porcine; [D-Ala²]-dynorphin A 1-9, porcine; [DArg⁶]-dynorphin A 1-13, porcine; [DArg⁸]-dynorphin A 1-13, porcine; [Des-Tyr¹]-

dynorphin A 1-8; [D-Pro¹⁰]-dynorphin A 1-11, porcine; dynorphin A amide, porcine; dynorphin A 1-6, porcine; dynorphin A 1-7, porcine; dynorphin A 1-8, porcine; dynorphin A 1-9, porcine; dynorphin A 1-10, porcine; dynorphin A 1-10 amide, porcine; dynorphin A 1-11, porcine; dynorphin A 1-12, porcine; dynorphin A 1-13, porcine; dynorphin A 1-13 amide, porcine; DAKLI (dynorphin A-analogue kappa ligand); DAKLI-biotin ([Arg^{11,13}]-dynorphin A (1-13)-Gly-NH(CH₂)₅NH-biotin); dynorphin A 2-17, porcine; dynorphin 2-17, amide, porcine; dynorphin A 2-12, porcine; dynorphin A 3-17, amide, porcine; dynorphin A 3-8, porcine; dynorphin A 3-13, porcine; dynorphin A 3-17, porcine; dynorphin A 7-17, porcine; dynorphin A 8-17, porcine; dynorphin A 6-17, porcine; dynorphin A 13-17, porcine; dynorphin A (prodynorphin 209-225), porcine; dynorphin B 1-9; [MeTyr¹, MeArg⁷, D-Leu⁸]-dynorphin 1-8 ethyl amide; [(nMe)Tyr¹] dynorphin A 1-13, amide, porcine; [Phe⁷]-dynorphin A 1-7, porcine; [Phe⁷]-dynorphin A 1-7, amide, porcine; and prodynorphin 228-256 (dynorphin B 29) (leumorphin), porcine.

Endorphin peptides including, but not limited to, alpha-neo-endorphin, porcine; beta-neo-endorphin; Ac-beta-endorphin, camel, bovine, ovine; Ac-beta-endorphin 1-27, camel, bovine, ovine; Ac-beta-endorphin, human; Ac-beta-endorphin 1-26, human; Ac-beta-endorphin 1-27, human; Ac-gamma-endorphin (Ac-beta-lipotropin 61-77); acetyl-alpha-endorphin; alpha-endorphin (beta-lipotropin 61-76); alpha-neo-endorphin analog; alpha-neo-endorphin 1-7; [Arg⁸]-alpha-neo-endorphin 1-8; beta-endorphin (beta-lipotropin 61-91), camel, bovine, ovine; beta-endorphin 1-27, camel, bovine, ovine; beta-endorphin, equine; beta-endorphin (beta-lipotropin 61-91), human; beta-endorphin (1-5) + (16-31), human; beta-endorphin 1-26, human; beta-endorphin 1-27, human; beta-endorphin 6-31, human; beta-endorphin 18-31, human; beta-endorphin, porcine; beta-endorphin, rat; beta-lipotropin 1-10, porcine; beta-lipotropin 60-65; beta-lipotropin 61-64; beta-lipotropin 61-69; beta-lipotropin 88-91; biotinyl-beta-endorphin (biotinyl-beta-lipotropin 61-91); biocytin-beta-endorphin, human; gamma-endorphin (beta-lipotropin 61-77); [DAla²]-alpha-neo-endorphin 1-2, amide; [DAla²]-beta-lipotropin 61-69; [DAla²]-gamma-endorphin; [Des-Tyr¹]-beta-endorphin, human; [Des-Tyr¹]-gamma-endorphin (beta-lipotropin 62-77); [Leu⁵]-beta-endorphin, camel, bovine, ovine; [Met⁵, Lys⁶]-alpha-neo-endorphin 1-6; [Met⁵, Lys^{6,7}]-alpha-neo-endorphin 1-7; and [Met⁵, Lys⁶, Arg⁷]-alpha-neo-endorphin 1-7.

Endothelin peptides including, but not limited to, endothelin-1 (ET-1); endothelin-1 [Biotin-Lys⁹]; endothelin-1 (1-15), human; endothelin-1 (1-15), amide, human; Ac-

endothelin-1 (16-21), human; Ac-[DTrip¹⁶]-endothelin-1 (16-21), human; [Ala^{3,11}]-endothelin-1; [Dprl, Asp¹⁵]-endothelin-1; [Ala²]-endothelin-3, human; [Ala¹⁸]-endothelin-1, human; [Asn¹⁸]-endothelin-1, human; [Res-701-1]-endothelin B receptor antagonist; Suc-[Glu⁹, Ala^{11,15}]-endothelin-1 (8-21), IRL-1620; endothelin-C-terminal hexapeptide; [D-Val²²]-big
 5 endothelin-1 (16-38), human; endothelin-2 (ET-2), human, canine; endothelin-3 (ET-3), human, rat, porcine, rabbit; biotinyl-endothelin-3 (biotinyl-ET-3); prepro-endothelin-1 (94-109), porcine; BQ-518; BQ-610; BQ-788; endothelium-dependent relaxation antagonist; FR139317; IRL-1038; JKC-30 1; JKC-302; PD-145065; PD 142893; sarafotoxin S6a (atractaspis engaddensis); sarafotoxin S6b (atractaspis engaddensis); sarafotoxin S6c (atractaspis engaddensis); [Lys⁴]-sarafotoxin S6c; sarafotoxin S6d; big endothelin-1, human;
 10 biotinyl-big endothelin-1, human; big endothelin-1 (1-39), porcine; big endothelin-3 (22-41), amide, human; big endothelin-1 (22-39), rat; big endothelin-1 (1-39), bovine; big endothelin-1 (22-39), bovine; big endothelin-1 (19-38), human; big endothelin-1 (22-38), human; big endothelin-2, human; big endothelin-2 (22-37), human; big endothelin-3, human; big
 15 endothelin-1, porcine; big endothelin-1 (22-39) (prepro-endothelin-1 (74-91)); big endothelin-1, rat; big endothelin-2 (1-38), human; big endothelin-2 (22-38), human; big endothelin-3, rat; biotinyl-big endothelin-1, human; and [Tyr¹²³]-prepro-endothelin (110-130), amide, human.

ETa receptor antagonist peptides including, but not limited to, [BQ-123];
 20 [BE18257B]; [BE-18257A]/[W-7338A]; [BQ-485]; FR139317; PD-151242; and TTA-386.
 ETb receptor antagonist peptides including, but not limited to, [BQ-3020]; [RES-701-3]; and [IRL-1720]

Enkephalin peptides including, but not limited to, adrenorphin, free acid; amidorphin (proenkephalin A (104-129)-NH₂), bovine; BAM-12P (bovine adrenal medulla
 25 dodecapeptide); BAM-22P (bovine adrenal medulla docosapeptide); benzoyl-Phe- Ala-Arg; enkephalin; [D-Ala², D-Leu⁵]-enkephalin; [D-Ala², D-Met⁵]-enkephalin; [DAla²]-Leu-enkephalin, amide; [DAla², Leu⁵, Arg⁶]-enkephalin; [Des-Tyr¹, DPen^{2,5}]-enkephalin; [Des-Tyr¹, DPen², Pen⁵]-enkephalin; [Des-Tyr¹]-Leu-enkephalin; [D-Pen^{2,5}]-enkephalin; [DPen², Pen⁵]-enkephalin; enkephalinase substrate; [D-Pen², pCI-Phe⁴, D-Pen⁵]-enkephalin; Leu-
 30 enkephalin; Leu-enkephalin, amide; biotinyl-Leu-enkephalin; [D-Ala²]-Leu-enkephalin; [D-Ser²]-Leu-enkephalin-Thr (delta-receptor peptide) (DSLET); [D-Thr²]-Leu-enkephalin-Thr (DTLET); [Lys⁶]-Leu-enkephalin; [Met⁵, Arg⁶]-enkephalin; [Met⁵, Arg⁶]-enkephalin-Arg;

[Met⁵,Arg⁶,Phe⁷]-enkephalin, amide; Met-enkephalin; biotinyl-Met-enkephalin; [D-Ala²]-Met-enkephalin; [D-Ala²]-Met-enkephalin, amide; Met-enkephalin-Arg-Phe; Met-enkephalin, amide; [Ala²]-Met-enkephalin, amide; [DMet²,Pro⁵]-enkephalin, amide; [DTrp²]-Met-enkephalin, amide, metorphinamide (adrenorphin); peptide B, bovine; 3200-Dalton adrenal peptide E, bovine; peptide F, bovine; preproenkephalin B 186-204, human; spinorphin, bovine; and thiorphan (D, L, 3-mercapto-2-benzylpropanoyl-glycine).

Fibronectin peptides including, but not limited to platelet factor-4 (58-70), human; echistatin (*Echis carinatus*); E, P, L selectin conserved region; fibronectin analog; fibronectin-binding protein; fibrinopeptide A, human; [Tyr⁰]-fibrinopeptide A, human; fibrinopeptide B, human; [Glu¹]-fibrinopeptide B, human; [Tyr¹⁵]-fibrinopeptide B, human; fibrinogen beta-chain fragment of 24-42; fibrinogen binding inhibitor peptide; fibronectin related peptide (collagen binding fragment); fibrinolysis inhibiting factor; FN-C/H-1 (fibronectin heparin-binding fragment); FN-C/H-V (fibronectin heparin-binding fragment); heparin-binding peptide; laminin penta peptide, amide; Leu-Asp-Val-NH₂ (LDV-NH₂), human, bovine, rat, chicken; necrofibrin, human; necrofibrin, rat; and platelet membrane glycoprotein IIB peptide 296-306.

Galanin peptides including, but not limited to, galanin, human; galanin 1-19, human; preprogalanin 1-30, human; preprogalanin 65-88, human; preprogalanin 89-123, human; galanin, porcine; galanin 1-16, porcine, rat; galanin, rat; biotinyl-galanin, rat; preprogalanin 28-67, rat; galanin 1-13-bradykinin 2-9, amide; M40, galanin 1-13-Pro-Pro-(Ala-Leu) 2-Ala-amide; C7, galanin 1-13-spantide-amide; GMAP 1-41, amide; GMAP 16-41, amide; GMAP 25-41, amide; galantide; and entero-kassinin.

Gastrin peptides including, but not limited to, gastrin, chicken; gastric inhibitory peptide (GIP), human; gastrin I, human; biotinyl-gastrin I, human; big gastrin-1, human; gastrin releasing peptide, human; gastrin releasing peptide 1-16, human; gastric inhibitory polypeptide (GIP), porcine; gastrin releasing peptide, porcine; biotinyl-gastrin releasing peptide, porcine; gastrin releasing peptide 14-27, porcine, human; little gastrin, rat; pentagastrin; gastric inhibitory peptide 1-30, porcine; gastric inhibitory peptide 1-30, amide, porcine; [Tyr⁰]-gastric inhibitory peptide 23-42, human; and gastric inhibitory peptide, rat.

Glucagon peptides including, but not limited to, [Des-His¹,Glu⁹]-glucagon, extendin-4, glucagon, human; biotinyl-glucagon, human; glucagon 19-29, human; glucagon 22-29, human; Des-His¹-[Glu⁹]-glucagon, amide; glucagon-like peptide 1, amide (preproglucagon

72-107, amide); glucagon-like peptide 1 (preproglucagon 72-108), human; glucagon-like peptide 1 (7-36) (preproglucagon 78-107, amide); glucagon-like peptide II, rat; biotinyl-glucagon-like peptide-1 (7-36) (biotinyl-preproglucagon 78-107, amide); glucagon-like peptide 2 (preproglucagon 126-159), human; oxyntomodulin/glucagon 37; and valosin (peptide VQY), porcine.

Gn-RH associated peptides (GAP) including, but not limited to, Gn-RH associated peptide 25-53, human; Gn-RH associated peptide 1-24, human; Gn-RH associated peptide 1-13, human; Gn-RH associated peptide 1-13, rat; gonadotropin releasing peptide, follicular, human; [Tyr⁰]-GAP ([Tyr⁰]-Gn-RH Precursor Peptide 14-69), human; and proopiomelanocortin (POMC) precursor 27-52, porcine.

Growth factor peptides including, but not limited to, cell growth factors; epidermal growth factors; tumor growth factor; alpha-TGF; beta-TF; alpha-TGF 34-43, rat; EGF, human; acidic fibroblast growth factor; basic fibroblast growth factor; basic fibroblast growth factor 13-18; basic fibroblast growth factor 120-125; brain derived acidic fibroblast growth factor 1-11; brain derived basic fibroblast growth factor 1-24; brain derived acidic fibroblast growth factor 102-111; [Cys(Acm^{20,31})]-epidermal growth factor 20-31; epidermal growth factor receptor peptide 985-996; insulin-like growth factor (IGF)-I, chicken; IGF-I, rat; IGF-I, human; Des (1-3) IGF-I, human; R3 IGF-I, human; R3 IGF-I, human; long R3 IGF-I, human; adjuvant peptide analog; anorexigenic peptide; Des (1-6) IGF-II, human; R6 IGF-II, human; IGF-I analogue; IGF I (24-41); IGF I (57-70); IGF I (30-41); IGF II; IGF II (33-40); [Tyr⁰]-IGF II (33-40); liver cell growth factor; midkine; midkine 60-121, human; N-acetyl, alpha-TGF 34-43, methyl ester, rat; nerve growth factor (NGF), mouse; platelet-derived growth factor; platelet-derived growth factor antagonist; transforming growth factor-alpha, human; and transforming growth factor-I, rat.

Growth hormone peptides including, but not limited to, growth hormone (hGH), human; growth hormone 1-43, human; growth hormone 6-13, human; growth hormone releasing factor, human; growth hormone releasing factor, bovine; growth hormone releasing factor, porcine; growth hormone releasing factor 1-29, amide, rat; growth hormone pro-releasing factor, human; biotinyl-growth hormone releasing factor, human; growth hormone releasing factor 1-29, amide, human; [D-Ala²]-growth hormone releasing factor 1-29, amide, human; [N-Ac-Tyr¹, D-Arg²]-GRF 1-29, amide; [His¹, Nle²⁷]-growth hormone releasing factor 1-32, amide; growth hormone releasing factor 1-37, human; growth hormone releasing

factor 1-40, human; growth hormone releasing factor 1-40, amide, human; growth hormone releasing factor 30-44, amide, human; growth hormone releasing factor, mouse; growth hormone releasing factor, ovine; growth hormone releasing factor, rat; biotinyl- growth hormone releasing factor, rat; GHRP-6 ([His¹, Lys⁶]-GHRP); hexarelin (growth hormone releasing hexapeptide); and [D-Lys³]-GHRP-6.

GTP-binding protein fragment peptides including, but not limited to, [Arg⁸]-GTP-binding protein fragment, Gs alpha; GTP-binding protein fragment, G beta; GTP-binding protein fragment, GAlpha; GTP-binding protein fragment, Go Alpha; GTP-binding protein fragment, Gs Alpha; and GTP-binding protein fragment, G Alpha i2.

Guanylin peptides including, but not limited to, guanylin, human; guanylin, rat; and uroguanylin.

Inhibin peptides including, but not limited to, inhibin, bovine; inhibin, alpha-subunit 1-32, human; [Tyr⁰]-inhibin, alpha-subunit 1-32, human; seminal plasma inhibin-like peptide, human; [Tyr⁰]-seminal plasma inhibin-like peptide, human; inhibin, alpha-subunit 1-32, porcine; and [Tyr⁰]-inhibin, alpha-subunit 1-32, porcine.

Insulin peptides including, but not limited to, insulin, human; insulin, porcine; IGF-I, human; insulin-like growth factor II (69-84); pro-insulin-like growth factor II (68-102), human; pro-insulin-like growth factor II (105-128), human; [Asp^{B28}]-insulin, human; [Lys^{B28}]-insulin, human; [Leu^{B28}]-insulin, human; [Val^{B28}]-insulin, human; [Ala^{B28}]-insulin, human; [Asp^{B28}, Pro^{B29}]-insulin, human; [Lys^{B28}, Pro^{B29}]-insulin, human; [Leu^{B28}, Pro^{B29}]-insulin, human; [Val^{B28}, Pro^{B29}]-insulin, human; and [Ala^{B28}, Pro^{B29}]-insulin, human, B22-B30 insulin, human; B23-B30 insulin, human; B25-B30 insulin, human; B26-B30 insulin, human; B27-B30 insulin, human; B29-B30 insulin, human; the A chain of human insulin, and the B chain of human insulin.

Interleukin peptides including, but not limited to, interleukin-1 beta 165-181, rat; and interleukin-8 (IL-8, CINC/gro), rat.

Laminin peptides including, but not limited to, laminin; alpha1 (I)-CB3 435-438, rat; and laminin binding inhibitor.

Leptin peptides including, but not limited to, leptin 93-105, human; leptin 22-56, rat; Tyr-leptin 26-39, human; and leptin 116-130, amide, mouse.

Leucokinin peptides including, but not limited to, leucomyosuppressin (LMS); leucopyrokinin (LPK); leucokinin I; leucokinin II; leucokinin III; leucokinin IV; leucokinin VI; leucokinin VII; and leucokinin VIII.

Luteinizing hormone-releasing hormone peptides including, but not limited to, antide;
 5 Gn-RH II, chicken; luteinizing hormone-releasing hormone (LH-RH) (GnRH); biotinyl-LH-RH; cetrorelix (D-20761); [D-Ala⁶]-LH-RH; [Gln⁸]-LH-RH (Chicken LH-RH); [DLeu⁶, Val⁷] LH-RH 1-9, ethyl amide; [D-Lys⁶]-LH-RH; [D-Phe², Pro³, D-Phe⁶]-LH-RH; [DPhe², DAla⁶] LH-RH; [Des-Gly¹⁰]-LH-RH, ethyl amide; [D-Ala⁶, Des-Gly¹⁰]-LH-RH, ethyl amide; [DTrp⁶]-LH-RH, ethyl amide; [D-Trp⁶, Des-Gly¹⁰]-LH-RH, ethyl amide (Deslorelin);
 10 [DSer(But)⁶, Des-Gly¹⁰]-LH-RH, ethyl amide; ethyl amide; leuprolide; LH-RH 4-10; LH-RH 7-10; LH-RH, free acid; LH-RH, lamprey; LH-RH, salmon; [Lys⁸]-LH-RH; [Trp⁷, Leu⁸] LH-RH, free acid; and [(t-Bu)DSer⁶, (Aza)Gly¹⁰]-LH-RH.

Mastoparan peptides including, but not limited to, mastoparan; mas7; mas8; mas17; and mastoparan X.

15 Mast cell degranulating peptides including, but not limited to, mast cell degranulating peptide HR-1; and mast cell degranulating peptide HR-2.

Melanocyte stimulating hormone (MSH) peptides including, but not limited to, [Ac-Cys⁴, DPhe⁷, Cys¹⁰] alpha-MSH 4-13, amide; alpha-melanocyte stimulating hormone; alpha-MSH, free acid; beta-MSH, porcine; biotinyl-alpha-melanocyte stimulating hormone;
 20 biotinyl-[Nle⁴, D-Phe⁷] alpha-melanocyte stimulating hormone; [Des -Acetyl]-alpha-MSH; [DPhe⁷]-alpha-MSH, amide; gamma-1-MSH, amide; [Lys⁰]-gamma-1-MSH, amide; MSH release inhibiting factor, amide; [Nle⁴]-alpha-MSH, amide; [Nle⁴, D-Phe⁷]-alpha-MSH; N-Acetyl, [Nle⁴, DPhe⁷] alpha-MSH 4-10, amide; beta-MSH, human; and gamma-MSH.

Morphiceptin peptides including, but not limited to, morphiceptin (beta-casomorphin
 25 1-4 amide); [D-Pro⁴]-morphiceptin; and [N-MePhe³, D-Pro⁴]-morphiceptin.

Motilin peptides including, but not limited to, motilin, canine; motilin, porcine; biotinyl-motilin, porcine; and [Leu¹³]-motilin, porcine.

Neuro-peptides including, but not limited to, Ac-Asp-Glu; achatina cardio-excitatory peptide-1 (ACEP-1) (Achatina fulica); adipokinetic hormone (AKH) (Locust); adipokinetic
 30 hormone (Heliothis zea and Manduca sexta); alytesin; Tabanus atratus adipokinetic hormone (Taa-AKH); adipokinetic hormone II (Locusta migratoria); adipokinetic hormone II (Schistocera gregaria); adipokinetic hormone III (AKH-3); adipokinetic hormone G (AKH-

- G) (*Gryllus bimaculatus*); allatotropin (AT) (*Manduca sexta*); allatotropin 6-13 (*Manduca sexta*); APGW amide (*Lymnaea stagnalis*); buccalin; cerebellin; [Des-Ser¹]-cerebellin; corazonin (American Cockroach *Periplaneta americana*); crustacean cardioactive peptide (CCAP); crustacean erythrophore; DF2 (*Procambarus clarkii*); diazepam-binding inhibitor fragment, human; diazepam binding inhibitor fragment (ODN); eleodoisin related peptide; FMRF amide (molluscan cardioexcitatory neuro-peptide); Gly-Pro-Glu (GPE), human; granuliberin R; head activator neuropeptide; [His⁷]-corazonin; stick insect hypertrehalosaemic factor II; *Tabanus atratus* hypotrehalosemic hormone (Taa-HoTH); isoguvacine hydrochloride; bicuculline methiodide; piperidine-4-sulphonic acid; joining peptide of proopiomelanocortin (POMC), bovine; joining peptide, rat; KSAYMRF amide (*P. redivivus*); kassinin; kinetensin; levitide; litorin; LUQ 81-91 (*Aplysia californica*); LUQ 83-91 (*Aplysia californica*); myoactive peptide I (*Periplaneta* CC-1) (Neuro-hormone D); myoactive peptide II (*Periplaneta* CC-2); myomodulin; neuron specific peptide; neuron specific enolase 404-443, rat; neuropeptide FF; neuropeptide K, porcine; NEI (prepro-MCH 131-143) neuropeptide, rat; NGE (prepro-MCH 110-128) neuropeptide, rat; NFI (*Procambarus clarkii*); PBAN-I (*Bombyx mori*); Hez-PBAN (*Heliothis zea*); SCPB (cardioactive peptide from *Aplysia*); secretoneurin, rat; uperolein; urechistachykinin I; urechistachykinin II; xenopsin-related peptide I; xenopsin-related peptide II; pedal peptide (Pep), *Aplysia*; peptide FI, lobster; phyllomedusin; polistes mastoparan; proctolin; ranatensin; Ro I (Lubber Grasshopper, *Romalea microptera*); Ro II (Lubber Grasshopper, *Romalea microptera*); SALMF amide 1 (S1); SALMF amide 2 (S2); and SCPA.

- Neuropeptide Y (NPY) peptides including, but not limited to, [Leu³¹,Pro³⁴]-neuropeptide Y, human; neuropeptide F (*Moniezia expansa*); B1BP3226 NPY antagonist; Bis (31/31') {[Cys³¹, Trp³², Nva³⁴] NPY 31-36}; neuropeptide Y, human, rat; neuropeptide Y 1-24 amide, human; biotinyl-neuropeptide Y; [D-Tyr^{27,36}, D-Thr³²]-NPY 27-36; Des 10-17 (cyclo 7-21) [Cys^{7,21}, Pro³⁴]-NPY; C2-NPY; [Leu³¹, Pro³⁴] neuropeptide Y, human; neuropeptide Y, free acid, human; neuropeptide Y, free acid, porcine; prepro NPY 68-97, human; N-acetyl-[Leu²⁸, Leu³¹] NPY 24-36; neuropeptide Y, porcine; [D-Trp³²]-neuropeptide Y, porcine; [D-Trp³²] NPY 1-36, human; [Leu¹⁷, DTrp³²] neuropeptide Y, human; [Leu³¹, Pro³⁴]-NPY, porcine; NPY 2-36, porcine; NPY 3-36, human; NPY 3-36, porcine; NPY 13-36, human; NPY 13-36, porcine; NPY 16-36, porcine; NPY 18-36, porcine; NPY 20-36;

IFY 22-36; NPY 26-36; [Pro³⁴]-NPY 1-36, human; [Pro³⁴]-neuropeptide Y, porcine; PYX-1; PYX-2; T4-[NPY(33-36)]4; and Tyr(OMe)²¹-neuropeptide Y, human.

Neurotropic factor peptides including, but not limited to, glial derived neurotrophic factor (GDNF); brain derived neurotrophic factor (BDNF); and ciliary neurotrophic factor (CNTF).

Orexin peptides including, but not limited to, orexin A; orexin B, human; orexin B, rat, mouse.

Opioid peptides including, but not limited to, alpha-casein fragment 90-95; BAM-18P; casomokinin L; casoxin D; crystalline; DALDA; dermenkephalin (deltorphan) (Phylomedusa sauvagei); [D-Ala²]-deltorphan I; [D-Ala²]-deltorphan II; endomorphin-1; endomorphin-2; kyotorphan; [DArg²]-kyotorphan; morphin tolerance peptide; morphine modulating peptide, C-terminal fragment; morphine modulating neuropeptide (A-18-F-NH₂); nociceptin [orphanin FQ] (ORL1 agonist); TIPP; Tyr-MIF-1; Tyr-W-MIF-1; valorphin; LW-hemorphin-6, human; Leu-valorphin-Arg; and Z-Pro-D-Leu.

Oxytocin peptides including, but not limited to, [Asu⁶]-oxytocin; oxytocin; biotinyl-oxytocin; [Thr⁴, Gly⁷]-oxytocin; and tocinoic acid ([Ile³]-pressinoic acid).

PACAP (pituitary adenylating cyclase activating peptide) peptides including, but not limited to, PACAP 1-27, human, ovine, rat; PACAP (1-27)-Gly-Lys-Arg-NH₂, human; [Des-Gln¹⁶]-PACAP 6-27, human, ovine, rat; PACAP38, frog; PACAP27-NH₂, human, ovine, rat; biotinyl-PACAP27-NH₂, human, ovine, rat; PACAP 6-27, human, ovine, rat; PACAP38, human, ovine, rat; biotinyl-PACAP38, human, ovine, rat; PACAP 6-38, human, ovine, rat; PACAP27-NH₂, human, ovine, rat; biotinyl-PACAP27-NH₂, human, ovine, rat; PACAP 6-27, human, ovine, rat; PACAP38, human, ovine, rat; biotinyl-PACAP38, human, ovine, rat; PACAP 6-38, human, ovine, rat; PACAP38 16-38, human, ovine, rat; PACAP38 31-38, human, ovine, rat; PACAP38 31-38, human, ovine, rat; PACAP-related peptide (PRP), human; and PACAP-related peptide (PRP), rat.

Pancreastatin peptides including, but not limited to, chromostatin, bovine; pancreastatin (hPST-52) (chromogranin A 250-301, amide); pancreastatin 24-52 (hPST-29), human; chromogranin A 286-301, amide, human; pancreastatin, porcine; biotinyl-pancreastatin, porcine; [Nle⁸]-pancreastatin, porcine; [Tyr⁰,Nle⁸]-pancreastatin, porcine; [Tyr⁰]-pancreastatin, porcine; parastatin 1-19 (chromogranin A 347-365), porcine; pancreastatin (chromogranin A 264-314-amide, rat; biotinyl-pancreastatin (biotinyl-

chromogranin A 264-314-amide; [Tyr⁰]-pancreastatin, rat; pancreastatin 26-51, rat; and pancreastatin 33-49, porcine.

Pancreatic polypeptides including, but not limited to, pancreatic polypeptide, avian; pancreatic polypeptide, human; C-fragment pancreatic polypeptide acid, human; C-fragment
 5 pancreatic polypeptide amide, human; pancreatic polypeptide (*Rana temporaria*); pancreatic polypeptide, rat; and pancreatic polypeptide, salmon.

Parathyroid hormone peptides including, but not limited to, [Asp⁷⁶]-parathyroid hormone 39-84, human; [Asp⁷⁶]-parathyroid hormone 53-84, human; [Asn⁷⁶]-parathyroid hormone 1-84, hormone; [Asn⁷⁶]-parathyroid hormone 64-84, human; [Asn⁸, Leu¹⁸]-
 10 parathyroid hormone 1-34, human; [Cys^{5,28}]-parathyroid hormone 1-34, human; hypercalcemia malignancy factor 1-40; [Leu¹⁸]-parathyroid hormone 1-34, human; [Lys(biotinyl)¹³, Nle^{8,18}, Tyr³⁴]-parathyroid hormone 1-34 amide; [Nle^{8,18}, Tyr³⁴]-parathyroid hormone 1-34 amide; [Nle^{8,18}, Tyr³⁴]-parathyroid hormone 3-34 amide, bovine; [Nle^{8,18}, Tyr³⁴]-parathyroid hormone 1-34, human; [Nle^{8,18}, Tyr³⁴]-parathyroid hormone 1-34 amide,
 15 human; [Nle^{8,18}, Tyr³⁴]-parathyroid hormone 3-34 amide, human; [Nle^{8,18}, Tyr³⁴]-parathyroid hormone 7-34 amide, bovine; [Nle^{8,21}, Tyr³⁴]-parathyroid hormone 1-34 amide, rat; parathyroid hormone 44-68, human; parathyroid hormone 1-34, bovine; parathyroid hormone 3-34, bovine; parathyroid hormone 1-31 amide, human; parathyroid hormone 1-34, human; parathyroid hormone 13-34, human; parathyroid hormone 1-34, rat; parathyroid hormone 1-
 20 38, human; parathyroid hormone 1-44, human; parathyroid hormone 28-48, human; parathyroid hormone 39-68, human; parathyroid hormone 39-84, human; parathyroid hormone 53-84, human; parathyroid hormone 69-84, human; parathyroid hormone 70-84, human; [Pro³⁴]-peptide YY (PYY), human; [Tyr⁰]-hypercalcemia malignancy factor 1-40; [Tyr⁰]-parathyroid hormone 1-44, human; [Tyr⁰]-parathyroid hormone 1-34, human; [Tyr¹]-
 25 parathyroid hormone 1-34, human; [Tyr²⁷]-parathyroid hormone 27-48, human; [Tyr³⁴]-parathyroid hormone 7-34 amide, bovine; [Tyr⁴³]-parathyroid hormone 43-68, human; [Tyr⁵², Asn⁷⁶]-parathyroid hormone 52-84, human; and [Tyr⁶³]-parathyroid hormone 63-84, human.

Parathyroid hormone (PTH)-related peptides including, but not limited to, PTHrP ([Tyr³⁶]-PTHrP 1-36 amide), chicken; hHCF-(1-34)-NH₂ (humoral hypercalcemic factor),
 30 human; PTH-related protein 1-34, human; biotinyl-PTH-related protein 1-34, human; [Tyr⁰]-PTH-related protein 1-34, human; [Tyr³⁴]-PTH-related protein 1-34 amide, human; PTH-related protein 1-37, human; PTH-related protein 7-34 amide, human; PTH-related protein

38-64 amide, human; PTH-related protein 67-86 amide, human; PTH-related protein 107-111, human, rat, mouse; PTH-related protein 107-111 free acid; PTH-related protein 107-138, human; and PTH-related protein 109-111, human.

Peptide T peptides including, but not limited to, peptide T; [D-Ala¹¹]-peptide T; and
5 [D-Ala¹]-peptide T amide.

Prolactin-releasing peptides including, but not limited to, prolactin-releasing peptide 31, human; prolactin-releasing peptide 20, human; prolactin-releasing peptide 31, rat; prolactin-releasing peptide 20, rat; prolactin-releasing peptide 31, bovine; and prolactin-releasing peptide 20, bovine.

10 Peptide YY (PYY) peptides including, but not limited to, PYY, human; PYY 3-36, human; biotinyl-PYY, human; PYY, porcine, rat; and [Leu³¹, Pro³⁴]-PYY, human.

Renin substrate peptides including, but not limited to, acetyl, angiotensinogen 1-14, human; angiotensinogen 1-14, porcine; renin substrate tetradecapeptide, rat; [Cys⁸]-renin substrate tetradecapeptide, rat; [Leu⁸]-renin substrate tetradecapeptide, rat; and [Val⁸]-renin
15 substrate tetradecapeptide, rat.

Secretin peptides including, but not limited to, secretin, canine; secretin, chicken; secretin, human; biotinyl-secretin, human; secretin, porcine; and secretin, rat.

Somatostatin (GIF) peptides including, but not limited to, BIM-23027; biotinyl-somatostatin; biotinylated cortistatin 17, human; cortistatin 14, rat; cortistatin 17, human; [Tyr⁰]-cortistatin 17, human; cortistatin 29, rat; [D-Trp⁸]-somatostatin; [D-Trp⁸, DCys¹⁴]-
20 somatostatin; [D-Trp⁸, Tyr¹¹]-somatostatin; [D-Trp¹¹]-somatostatin; NTB (Naltriben); [Nle⁸]-somatostatin 1-28; octreotide (SMS 201-995); prosomatostatin 1-32, porcine; [Tyr⁰]-somatostatin; [Tyr¹]-somatostatin; [Tyr¹]-somatostatin 28 (1-14); [Tyr¹¹]-somatostatin; [Tyr⁰, D-Trp⁸]-somatostatin; somatostatin; somatostatin antagonist; somatostatin-25; somatostatin-
25 28; somatostatin 28 (1-12); biotinyl-somatostatin-28; [Tyr⁰]-somatostatin-28; [Leu⁸, D-Trp²², Tyr²⁵]-somatostatin-28; biotinyl-[Leu⁸, D-Trp²², Tyr²⁵]-somatostatin-28; somatostatin-28 (1-14); and somatostatin analog, RC-160.

Substance P peptides including, but not limited to, G protein antagonist-2; Ac-[Arg⁶, Sar⁹, Met(O2)¹¹]-substance P 6-11; [Arg³]-substance P; Ac-Trp-3,5-bis(trifluoromethyl) benzyl ester; Ac-[Arg⁶, Sar⁹, Met(O2)¹¹]-substance P 6-11; [D-Ala⁴]-substance P 4-11; [Tyr⁶, D-Phe⁷, D-His⁹]-substance P 6-11 (sendide); biotinyl-substance P; biotinyl-NTE[Arg³]-
30 substance P; [Tyr⁸]-substance P; [Sar⁹, Met(O2)¹¹]-substance P; [D-Pro², D-Trp^{7,9}]-substance

P; [D-Pro⁴, 0-Trp^{7,9}]-substance P 4-11; substance P 4-11; [DTrp^{2,7,9}]-substance P; [(Dehydro)Pro^{2,4}, Pro⁹]-substance P; [Dehydro-Pro⁴]-substance P 4-11; [Glp⁵, (Me)Phe⁸, Sar⁹]-substance P 5-11; [Glp⁵, Sar⁹]-substance P 5-11; [Glp⁵]-substance P 5-11; hepta-substance P (substance P 5-11); hexa-substance P (substance P 6-11); [MePhe⁸, Sar⁹]-substance P; [Nle¹¹]-substance P; Octa-substance P (substance P 4-11); [pGlu¹]-hexa-substance P ([pGlu⁶]-substance P 6-11); [pGlu⁶, D-Pro⁹]-substance P 6-11; [(pNO₂)Phe⁷Nle¹¹]-substance P; penta-substance P (substance P 7-11); [Pro⁹]-substance P; GR73632, substance P 7-11; [Sar⁴]-substance P 4-11; [Sar⁹]-substance P; septide ([pGlu⁶, Pro⁹]-substance P 6-11); spantide I; spantide II; substance P; substance P, cod; substance P, trout; substance P antagonist; substance P-Gly-Lys-Arg; substance P 1-4; substance P 1-6; substance P 1-7; substance P 1-9; deca-substance P (substance P 2-11); nona-substance P (substance P 3-11); substance P tetrapeptide (substance P 8-11); substance P tripeptide (substance P 9-11); substance P, free acid; substance P methyl ester; and [Tyr⁸, Nle¹¹] substance P.

Tachykinin peptides including, but not limited to, [Ala⁵, beta-Ala⁸] neurokinin A 4-10; eledoisin; locustatachykinin I (Lom-TK-I) (*Locusta migratoria*); locustatachykinin II (Lom-TK-II) (*Locusta migratoria*); neurokinin A 4-10; neurokinin A (neuromedin L, substance K); neurokinin A, cod and trout; biotinyl-neurokinin A (biotinyl-neuromedin L, biotinyl-substance K); [Tyr⁰]-neurokinin A; [Tyr⁶]-substance K; FR64349; [Lys³, Gly⁸-(R)-gamma-lactam-Leu⁹]-neurokinin A 3-10; GR83074; GR87389; GR94800; [Beta-Ala⁸]-neurokinin A 4-10; [Nle¹⁰]-neurokinin A 4-10; [Trp⁷, beta-Ala⁸]-neurokinin A 4-10; neurokinin B (neuromedin K); biotinyl-neurokinin B (biotinyl-neuromedin K); [MePhe⁷]-neurokinin B; [Pro⁷]-neurokinin B; [Tyr⁰]-neurokinin B; neuromedin B, porcine; biotinyl-neuromedin B, porcine; neuromedin B-30, porcine; neuromedin B-32, porcine; neuromedin B receptor antagonist; neuromedin C, porcine; neuromedin N, porcine; neuromedin (U-8), porcine; neuromedin (U-25), porcine; neuromedin U, rat; neuropeptide-gamma (gamma-preprotachykinin 72-92); PG-KII; phyllolitorin; [Leu⁸]-phyllolitorin (*Phyllomedusa sauvagei*); physalaemin; physalaemin 1-11; scyliorhinin II, amide, dogfish; senktide, selective neurokinin B receptor peptide; [Ser²]-neuromedin C; beta-preprotachykinin 69-91, human; beta-preprotachykinin 111-129, human; tachyplesin I; xenopsin; and xenopsin 25 (xenin 25), human.

Thyrotropin-releasing hormone (TRH) peptides including, but not limited to, biotinyl-thyrotropin-releasing hormone; [Glu¹]-TRH; His-Pro-diketopiperazine; [3-Me-His²]-TRH;

pGlu-Gln-Pro-amide; pGlu-His; [Phe²]-TRH; prepro TRH 53-74; prepro TRH 83-106; prepro-TRH 160-169 (Ps4, TRH-potentiating peptide); prepro-TRH 178-199; thyrotropin-releasing hormone (TRH); TRH, free acid; TRH-SH Pro; and TRH precursor peptide.

Toxin peptides including, but not limited to, omega-agatoxin TK; agelenin, (spider, 5 *Agelena opulenta*); apamin (honeybee, *Apis mellifera*); calcicudine (CaC) (green mamba, *Dendroaspis angusticeps*); calciseptine (black mamba, *Dendroaspis polylepis polylepis*); charybdotoxin (ChTX) (scorpion, *Leiurus quinquestriatus* var. *hebraeus*); chlorotoxin; conotoxin GI (marine snail, *Conus geographus*); conotoxin GS (marine snail, *Conus geographus*); conotoxin MI (Marine *Conus magus*); alpha-conotoxin EI, *Conus ermineus*; 10 alpha-conotoxin SIA; alpha-conotoxin Iml; alpha-conotoxin SI (cone snail, *Conus striatus*); micro-conotoxin GIIIB (marine snail, *Conus geographus*); omega-conotoxin GVIA (marine snail, *Conus geographus*); omega-conotoxin MVIIA (*Conus magus*); omega-conotoxin MVIIC (*Conus magus*); omega-conotoxin SVIB (cone snail, *Conus striatus*); endotoxin inhibitor; geographutoxin I (GTX-I) (μ -Conotoxin GIIIA); iberiotoxin (IbTX) (scorpion, 15 *Buthus tamulus*); kaliotoxin 1-37; kaliotoxin (scorpion, *Androctonus mauretanicus mauretanicus*); mast cell-degranulating peptide (MCD-peptide, peptide 401); margatoxin (MgTX) (scorpion, *Centruroides Margaritatus*); neurotoxin NSTX-3 (pupua new guinean spider, *Nephilia maculata*); PLTX-II (spider, *Plectreurys tristes*); scyllatoxin (leiurotoxin I); and stichodactyla toxin (ShK).

20 Vasoactive intestinal peptides (VIP/PHI) including, but not limited to, VIP, human, porcine, rat, ovine; VIP-Gly-Lys-Arg-NH₂; biotinyl-PHI (biotinyl-PHI-27), porcine; [Glp¹⁶] VIP 16-28, porcine; PHI (PHI-27), porcine; PHI (PHI-27), rat; PHM-27 (PHI), human; prepro VIP 81-122, human; preproVIP/PHM 111-122; prepro VIP/PHM 156-170; biotinyl-PHM-27 (biotinyl-PHI), human; vasoactive intestinal contractor (endothelin-beta); vasoactive 25 intestinal octacosapeptide, chicken; vasoactive intestinal peptide, guinea pig; biotinyl-VIP, human, porcine, rat; vasoactive intestinal peptide 1-12, human, porcine, rat; vasoactive intestinal peptide 10-28, human, porcine, rat; vasoactive intestinal peptide 11-28, human, porcine, rat, ovine; vasoactive intestinal peptide (cod, *Gadus morhua*); vasoactive intestinal peptide 6-28; vasoactive intestinal peptide antagonist; vasoactive intestinal peptide antagonist 30 ([Ac-Tyr¹, D-Phe²]-GHRF 1-29 amide); vasoactive intestinal peptide receptor antagonist (4-Cl-D-Phe⁶, Leu¹⁷]-VIP); and vasoactive intestinal peptide receptor binding inhibitor, L-8-K.

What is Claimed is:

1. A substantially monodispersed mixture of conjugates, each conjugate comprising a drug coupled to an oligomer that comprises a polyalkylene glycol moiety.
2. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 2, 3 or 4 polyalkylene glycol subunits.
3. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 5 or 6 polyalkylene glycol subunits.
4. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.
5. The mixture according to Claim 4, wherein the oligomer is covalently coupled to the drug.
6. The mixture according to Claim 4, wherein the oligomer further comprises a lipophilic moiety.
7. The mixture according to Claim 4, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.
8. The mixture according to Claim 7, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.
9. The mixture according to Claim 8, wherein the oligomer further comprises a lipophilic moiety.
10. The mixture according to Claim 7, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

11. The mixture according to Claim 10, wherein the polypropylene glycol moiety is uniform.
12. The mixture according to Claim 11, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.
13. The mixture according to Claim 1, wherein at least 96, 97, 98 or 99 percent of the conjugates in the mixture have the same molecular weight.
14. The mixture according to Claim 1, wherein the mixture is a monodispersed mixture.
15. The mixture according to Claim 1, wherein the mixture is a substantially purely monodispersed mixture.
16. The mixture according to Claim 1, wherein at least 96, 97, 98 or 99 percent of the conjugates in the mixture have the same molecular weight and the same molecular structure.
17. The mixture according to Claim 1, wherein the mixture is a purely monodispersed mixture.
18. The mixture according to Claim 17, wherein the oligomer is covalently coupled to the drug.
19. The mixture according to Claim 17, wherein the oligomer further comprises a lipophilic moiety.
20. The mixture according to Claim 17, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

21. The mixture according to Claim 20, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.
22. The mixture according to Claim 21, wherein the oligomer further comprises a lipophilic moiety.
23. The mixture according to Claim 20, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.
24. The mixture according to Claim 23, wherein the polypropylene glycol moiety is uniform.
25. The mixture according to Claim 24, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.
26. The mixture according to Claim 1, wherein the mixture has an *in vivo* activity that is greater than the *in vivo* activity of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the mixture.
27. The mixture according to Claim 1, wherein the mixture has an *in vitro* activity that is greater than the *in vitro* activity of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the mixture.
28. The mixture according to Claim 1, wherein the mixture has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the mixture.
29. The mixture according to Claim 1, wherein the mixture has an inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the mixture.

30. The mixture according to Claim 1, wherein the drug is a polypeptide.

31. The mixture according to Claim 30, wherein the polypeptide is selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin
10 peptides, dynorphin peptides, endorphin peptides, endothelin peptides, ETa receptor antagonist peptides, ETb receptor antagonist peptides, enkephalin peptides, fibronectin peptides, galanin peptides, gastrin peptides, glucagon peptides, Gn-RH associated peptides, growth factor peptides, growth hormone peptides, GTP-binding protein fragment peptides, guanylin peptides, inhibin peptides, insulin peptides, interleukin peptides, laminin peptides,
15 leptin peptides, leucokinin peptides, luteinizing hormone-releasing hormone peptides, mastoparan peptides, mast cell degranulating peptides, melanocyte stimulating hormone peptides, morphiceptin peptides, motilin peptides, neuro-peptides, neuropeptide Y peptides, neurotropic factor peptides, orexin peptides, opioid peptides, oxytocin peptides, PACAP peptides, pancreastatin peptides, pancreatic polypeptides, parathyroid hormone peptides,
20 parathyroid hormone-related peptides, peptide T peptides, prolactin-releasing peptides, peptide YY peptides, renin substrate peptides, secretin peptides, somatostatin peptides, substance P peptides, tachykinin peptides, thyrotropin-releasing hormone peptides, toxin peptides, vasoactive intestinal peptides, vasopressin peptides, and virus related peptides.

32. The mixture according to Claim 31, wherein the oligomer is covalently coupled to a nucleophilic residue of the polypeptide.

33. The mixture according to Claim 31, wherein the oligomer further comprises a lipophilic moiety.

34. The mixture according to Claim 31, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

35. The mixture according to Claim 34, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

36. The mixture according to Claim 35, wherein the oligomer further comprises a lipophilic moiety.

37. The mixture according to Claim 34, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

38. The mixture according to Claim 37, wherein the polypropylene glycol moiety is uniform.

39. The mixture according to Claim 38, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

40. The mixture according to Claim 1, wherein the oligomer is covalently coupled to the drug.

41. The mixture according to Claim 1, wherein the oligomer further comprises a lipophilic moiety.

42. The mixture according to Claim 1, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

43. The mixture according to Claim 42, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

44. The mixture according to Claim 43, wherein the oligomer further comprises a lipophilic moiety.

45. The mixture according to Claim 42, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

46. The mixture according to Claim 45, wherein the polypropylene glycol moiety is uniform.

47. The mixture according to Claim 46, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

48. The mixture according to Claim 1, wherein each conjugate comprises a plurality of oligomers.

49. The mixture according to Claim 48, wherein each oligomer in the plurality of oligomers is the same.

50. The mixture according to Claim 1, wherein the oligomer comprises a first polyalkylene glycol moiety covalently coupled to the drug by a non-hydrolyzable bond and a second polyalkylene glycol moiety covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond.

51. The mixture according to Claim 1, wherein the oligomer further comprises a lipophilic moiety covalently coupled to the second polyethylene glycol moiety.

52. The mixture according to Claim 1, wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

53. A pharmaceutical composition comprising:

the mixture according to Claim 1; and
a pharmaceutically acceptable carrier.

54. A mixture of conjugates each comprising a drug coupled to an oligomer that comprises a polyalkylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

55. The mixture according to Claim 54, wherein the standard deviation of the molecular weight distribution is less than about 14 Daltons.

56. The mixture according to Claim 54, wherein the standard deviation of the molecular weight distribution is less than about 11 Daltons.

57. The mixture according to Claim 54, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

58. The mixture according to Claim 57, wherein the lower alkyl polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

59. The mixture according to Claim 57, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

60. The mixture according to Claim 59, wherein the oligomer further comprises a lipophilic moiety.

61. The mixture according to Claim 57, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

62. The mixture according to Claim 61, wherein the polypropylene glycol moiety is uniform.

63. The mixture according to Claim 62, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

64. The mixture according to Claim 54, wherein the drug is a polypeptide selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin
10 peptides, dynorphin peptides, endorphin peptides, endothelin peptides, ETa receptor antagonist peptides, ETb receptor antagonist peptides, enkephalin peptides, fibronectin peptides, galanin peptides, gastrin peptides, glucagon peptides, Gn-RH associated peptides, growth factor peptides, growth hormone peptides, GTP-binding protein fragment peptides, guanylin peptides, inhibin peptides, insulin peptides, interleukin peptides, laminin peptides,
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20 parathyroid hormone-related peptides, peptide T peptides, prolactin-releasing peptides, peptide YY peptides, renin substrate peptides, secretin peptides, somatostatin peptides, substance P peptides, tachykinin peptides, thyrotropin-releasing hormone peptides, toxin peptides, vasoactive intestinal peptides, vasopressin peptides, and virus related peptides.

65. A mixture of conjugates each comprising a drug coupled to a polymer comprising a polyalkylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 \sum_{i=1}^n N_i - \left(\sum_{i=1}^n N_i M_i \right)^2}$$

5 wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

66. The mixture according to Claim 65, wherein the dispersity coefficient is greater than 100,000.

67. The mixture according to Claim 65, wherein the dispersity coefficient is greater than 500,000.

68. The mixture according to Claim 65, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

69. The mixture according to Claim 68, wherein the lower alkyl polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

70. The mixture according to Claim 68, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

71. The mixture according to Claim 70, wherein the oligomer further comprises a lipophilic moiety.

72. The mixture according to Claim 68, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

73. The mixture according to Claim 72, wherein the polypropylene glycol moiety is uniform.

74. The mixture according to Claim 73, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

75. The mixture according to Claim 65, wherein the drug is a polypeptide selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin
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20 parathyroid hormone-related peptides, peptide T peptides, prolactin-releasing peptides, peptide YY peptides, renin substrate peptides, secretin peptides, somatostatin peptides, substance P peptides, tachykinin peptides, thyrotropin-releasing hormone peptides, toxin peptides, vasoactive intestinal peptides, vasopressin peptides, and virus related peptides.

76. A mixture of conjugates in which each conjugate:
comprises a drug coupled to an oligomer; and
has the same number of polyalkylene glycol subunits.

77. The mixture according to Claim 76, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

78. The mixture according to Claim 77, wherein the lower alkyl polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

79. The mixture according to Claim 77, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

80. The mixture according to Claim 79, wherein the oligomer further comprises a lipophilic moiety.

81. The mixture according to Claim 77, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

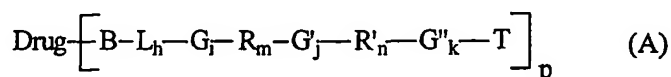
82. The mixture according to Claim 81, wherein the polypropylene glycol moiety is uniform.

83. The mixture according to Claim 82, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

84. The mixture according to Claim 76, wherein the drug is a polypeptide selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin

- 10 peptides, dynorphin peptides, endorphin peptides, endothelin peptides, ETa receptor antagonist peptides, ETb receptor antagonist peptides, enkephalin peptides, fibronectin peptides, galanin peptides, gastrin peptides, glucagon peptides, Gn-RH associated peptides, growth factor peptides, growth hormone peptides, GTP-binding protein fragment peptides, guanylin peptides, inhibin peptides, insulin peptides, interleukin peptides, laminin peptides, 15 leptin peptides, leucokinin peptides, luteinizing hormone-releasing hormone peptides, mastoparan peptides, mast cell degranulating peptides, melanocyte stimulating hormone peptides, morphiceptin peptides, motilin peptides, neuro-peptides, neuropeptide Y peptides, neurotropic factor peptides, orexin peptides, opioid peptides, oxytocin peptides, PACAP peptides, pancreastatin peptides, pancreatic polypeptides, parathyroid hormone peptides, 20 parathyroid hormone-related peptides, peptide T peptides, prolactin-releasing peptides, peptide YY peptides, renin substrate peptides, secretin peptides, somatostatin peptides, substance P peptides, tachykinin peptides, thyrotropin-releasing hormone peptides, toxin peptides, vasoactive intestinal peptides, vasopressin peptides, and virus related peptides.

85. A mixture of conjugates in which each conjugate has the same molecular weight and has the formula:



wherein:

- 5 B is a bonding moiety;
 L is a linker moiety;
 G, G' and G'' are individually selected spacer moieties;
 R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;
 10 T is a terminating moiety;
 h, i, j, k, m and n are individually 0 or 1, with the proviso that when R is the polyalkylene glycol moiety; m is 1, and when R' is the polyalkylene glycol moiety, n is 1; and
 p is an integer from 1 to the number of nucleophilic residues on the drug.

86. The mixture according to Claim 85, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene moiety.

87. The mixture according to Claim 86, wherein the lower alkyl polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

88. The mixture according to Claim 86, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

89. The mixture according to Claim 88, wherein:

R is the polyethylene glycol moiety;

R' is a lipophilic moiety;

n and m are 1; and

5 i, j and k are 0.

90. The mixture according to Claim 88, wherein:

R is a lipophilic moiety;

R' is the polyethylene glycol moiety;

n and m are 1; and

5 i, j and k are each 0.

91. The mixture according to Claim 86, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

92. The mixture according to Claim 91, wherein the polypropylene glycol moiety is uniform.

93. The mixture according to Claim 92, wherein:

R is the polypropylene glycol moiety;

m is 1;

i, j, k and n are each 0; and

5 each conjugate in the mixture is amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

94. The mixture according to Claim 85, wherein the drug is a polypeptide selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
 5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin
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 20 parathyroid hormone-related peptides, peptide T peptides, prolactin-releasing peptides, peptide YY peptides, renin substrate peptides, secretin peptides, somatostatin peptides, substance P peptides, tachykinin peptides, thyrotropin-releasing hormone peptides, toxin peptides, vasoactive intestinal peptides, vasopressin peptides, and virus related peptides.

95. A process for synthesizing a substantially monodispersed mixture of conjugates each conjugate comprising a drug coupled to an oligomer that comprises a polyethylene glycol moiety, said process comprising:

5 reacting a substantially monodispersed mixture comprising compounds having the structure of Formula I:



wherein R^1 is H or a lipophilic moiety; m is from 1 to 25; and X^+ is a positive ion,

with a substantially monodispersed mixture comprising compounds having the structure of
 10 Formula II:



wherein R^2 is H or a lipophilic moiety; and n is from 1 to 25,
 under conditions sufficient to provide a substantially monodispersed mixture comprising
 polymers having the structure of Formula III:



activating the substantially monodispersed mixture comprising polymers of Formula
 III to provide a substantially monodispersed mixture of activated polymers capable of
 reacting with a drug; and

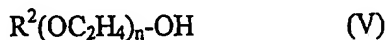
20 reacting the substantially monodispersed mixture of activated polymers with a
 substantially monodispersed mixture of drugs under conditions sufficient to provide a
 substantially monodispersed mixture of conjugates each comprising a drug coupled to an
 oligomer that comprises a polyethylene glycol moiety with m+n subunits.

96. The process according to Claim 95, wherein R^2 is a fatty acid moiety or an
 ester of a fatty acid moiety.

97. The process according to Claim 96, wherein the fatty acid moiety or the ester
 of a fatty acid moiety comprises an alkyl moiety at least 5 carbon atoms in length.

98. The process according to Claim 95, wherein R^1 is a methyl group.

99. The process according to Claim 95, further comprising:
 reacting a substantially monodispersed mixture comprising compounds having the
 structure of Formula V:



5 with a methanesulfonyl halide under conditions sufficient to provide a substantially
 monodispersed mixture comprising compounds having the structure of Formula II:

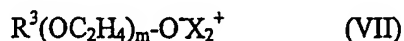


100. The process according to Claim 95, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula VI:



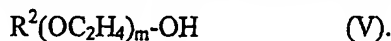
- 5 wherein R^2 is a lipophilic moiety;
with a substantially monodispersed mixture comprising compounds having the structure of Formula VII:



- wherein R^3 is benzyl, trityl, or THP; and X_2^+ is a positive ion;
10 under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula VIII:

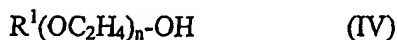


- reacting the substantially monodispersed mixture comprising compounds having the structure of Formula VIII under conditions sufficient to provide a substantially
15 monodispersed mixture comprising compounds having the structure of Formula V:

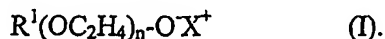


101. The process according to Claim 95, further comprising:

 reacting a substantially monodispersed mixture comprising compounds having the structure of Formula IV:



- 5 under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula I:



102. The process according to Claim 95, wherein the activating of the substantially monodispersed mixture comprises reacting the substantially monodispersed mixture of polymers of Formula III with N-hydroxy succinimide to provide an activated polymer capable of reacting with a drug.

103. The process according to Claim 95, wherein the drug is a polypeptide, and wherein the reacting of the substantially monodispersed mixture of activated polymers with a substantially monodispersed mixture of polypeptides comprises:

- 5 reacting the substantially monodispersed mixture of activated polymers with one or more amino functionalities of the polypeptide to provide a substantially monodispersed mixture of conjugates each comprising the polypeptide coupled to an oligomer that comprises a polyethylene glycol moiety with $m+n$ subunits.